UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 02-JUL-2013

Subject: **Fludioxonil.** Proposed Registration of New Formulation for Post-Harvest Application to Apples.

PC Code: 071503
Decision No.: 475789
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: 48996101

DP Barcode: D410480
Registration No.: 100-RLNL
Regulatory Action: Section 3 Registration
Case No.: 7017
CAS No.: 131341-86-1
40 CFR: §180.516

Reviewer: William D. Wassell, Chemist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED, 7509P)

Through: George F. Kramer, Ph.D., Senior Chemist
Dana Vogel, Acting Branch Chief
RAB1/HED (7509P)

To: Erin Malone/Shaja Joyner, RM 20
Registration Division (RD, 7505P)

Fludioxonil, 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile, is a contact fungicide, which inhibits protein kinase, leading to reduced fungal growth and development. Tolerances are currently established for residues of fludioxonil in/on various plant commodities at levels ranging from 0.01-500 ppm [40 CFR §180.516], including the pome fruit crop group (5.0 ppm). Scholar® 50 WP (EPA Reg. No. 100-969), a wettable powder (WP) consisting of 50% fludioxonil, is currently registered for postharvest use on pome fruit. Additionally, HED has recently recommended for the registration of the use of fludioxonil as a thermal electrofogger application to pome fruit.

CONCLUSIONS/RECOMMENDATIONS

As the submitted residue data are not adequate to demonstrate that the proposed thermal electrofogger use will not result in residues that exceed the established tolerance of 5.0 ppm for residues of fludioxonil in/on pome fruit, HED recommends against the proposed registration of Scholar® EZ for use on pome fruit.

DETAILED CONSIDERATIONS

Proposed & Registered Uses:

Registered Uses: Scholar® Fungicide (EPA Reg. No 100-969) and Scholar® SC Fungicide (EPA Reg. No. 100-1242) are registered for post harvest use on Pome Fruit. The currently registered uses on pome fruit are summarized in Table 1.

Table 1. Currently Registered Postharvest Uses for Scholar® Fungicide and Scholar® SC Fungicide.

Crop	Application Type	Rate	# Applications	Comments
Pome Fruit	High-Volume Spray	0.25 to 0.5 lb ai in 25-100 gallons of water	2	To treat 200,000 lbs of fruit (total of 0.16 oz ai per ton of fruit).
	Low-Volume Spray	0.25 to 0.5 lb ai in 7-25 gallons of water	2	
	Dip	0.25 to 0.5 lb ai in 100 gallons of water	2	Dip for ~30 sec.

The Scholar® labels state: For maximum decay control, treat fruit once before storage and once after storage, just prior to marketing.

Fludioxonil formulated as a 98% liquid formulation (eFOG-80 FDL Reg. No. 64864-67) is also registered for post-harvest application to pome fruit via thermal electrofogger. The registered use is summarized in Table 2.

Table 2. Currently Registered Thermal Electrofogger Use on Pome Fruit.

Crop	Application Type	Rate	# Applications	Comments
Pome Fruit	Thermal electrofogger	0.17 oz ai to treat 1 ton of fruit	1	Do not apply to fruit previously treated with fludioxonil via drench or dip/wash.

Proposed Use: Syngenta Crop Protection, LLC has proposed to register Scholar® EZ (EPA Reg. No. 100-RLNL), a 98% dry powder formulation of fludioxonil intended for thermal electrofogger use on pome fruit. The proposed use is summarized in Table 3.

Table 3. Proposed Thermal Electrofogger Use on Pome Fruit.

Crop	Application Type	Rate	# Applications	Comments
Pome Fruit	Thermal electrofogger	1 gram/bin (900 lb fruit per bin) [0.0048 lb ai/ton]	2	Apply within 24 hours of harvest. For maximum decay control during storage, treat fruit once before storage with Scholar EZ.

Residue Data (MRID No. 48996101): Syngenta Crop Protection, LLC has submitted residue data from a single post-harvest trial conducted during 2012 with fludioxonil on apples. Fludioxonil was applied post-harvest by thermal fogging to Sweet Tango apples in a simulated controlled-atmosphere cold storage warehouse at 0.00490 lb ai/ton of apples (2.45 g/metric ton).

Apples in separate rooms were treated with a 99% dry formulation of fludioxonil dissolved and suspended in propylene glycol with diphenylamine (TRT 1) or without diphenylamine (TRT 2). The untreated fruit samples were taken one day prior to application. Four treated samples from each treatment were sampled at an 18- to 20-hour post-treatment interval.

Samples of apple were analyzed for residues of fludioxonil using a liquid chromatograph equipped with tandem mass spectrometers (LC/MS/MS). The limit of quantification (LOQ), based on the lowest level of method validation (LLMV), was 0.01 ppm in/on apple. The method was adequate for data collection based on acceptable concurrent recoveries.

Following a post-harvest thermal fogging application of fludioxonil (99% dry formulation suspended in polypropylene glycol) with diphenylamine at 0.0049 lb ai/ton of apples, residues of fludioxonil were 0.391-0.684 ppm (n=4) with a mean of 0.491 ppm (standard deviation of 0.132 ppm) in/on apples collected 18-20 hours post treatment. Residues of fludioxonil were lower in/on apples treated at the same rate without the additive diphenylamine: 0.255-0.404 ppm (n=4) with a mean of 0.339 ppm (standard deviation of 0.066 ppm). The residue data is summarized in Table 4.

Table 4. Summary of Residue Data from Post-harvest Apple Trials with Fludioxonil.

Commodity	Method of Applic.	Total Applic. Rate (lb ai/ton)	Fludioxonil Residue Levels (ppm)[1]							
			n	Min.	Max.	LAFT[2]	HAFT[2]	Median	Mean	Std. Dev.
Apple, fruit	Post-harvest thermal fogging	0.0049 (+ diphenylamine)	4	0.391	0.684	NA	NA	0.445	0.491	0.132
		0.0049	4	0.255	0.404	NA	NA	0.348	0.339	0.066

[1] Because this study represents a post-harvest trial, statistical values were determined using residues in/on the replicate samples (determined with the quantification ion transition); n = number of samples.
[2] LAFT = lowest-average field trial. HAFT = highest-average field trial. NA = not applicable to this submission.

Conclusions: The results of this study are not adequate to show that residue levels on pome fruit will not exceed the established tolerance level. Fludioxonil is registered for post-harvest dip, drench, flood, or spray application to pome fruit. The proposed label states: "use Scholar EZ as a post-harvest dip, drench, flood, or spray for the control of post-harvest diseases…"; however, the proposed label does not include directions for use of Scholar® EZ as a post-harvest dip, drench, flood, or spray. It seems logical that the thermal fogging application within 24 hours of harvest is intended to replace the post-harvest dip, drench, flood, or spray application. If this is the case then, then the petitioner should add the following restriction to the label: "Do not apply to fruit previously treated with fludioxonil via drench or dip/wash." If the petitioner intends Scholar® EZ for both post-harvest drench or dip/wash and thermal fogging, then residue data reflecting both applications is required.

RDI: RAB1 Chem. Team: 06/19/2013
Petition Number: None
DP Barcode: 410480
PC Code: 071503

Primary Evaluator	William D. Wassell, Chemist Risk Assessment Branch 1 (RAB1) Health Effects Division (HED, 7509P)	Date: 02-JUL-2013
Approved by	George F. Kramer, Ph.D., Senior Chemist RAB1/HED (7509P)	Date: 02-JUL-2013

This data-evaluation record (DER) was originally prepared by Summitec Corporation (9724 Kingston Pike, Suite 602, Knoxville, TN 37922; submitted 5/29/13) and subcontractor CSS-Dynamac Corporation (10301 Democracy Lane, Suite 300, Fairfax, VA 22030). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

48996101 Mallipudi, N. M. (2013) Fludioxonil (CGA173506C) Magnitude of the Residue of Fludioxonil on Pome Fruit Following Post-Harvest Application by Fogging – Final Report: Lab Report Number: 35311; Task Number: TK0171667. Unpublished study prepared by Syngenta Crop Protection, LLC. 125 pages.

EXECUTIVE SUMMARY:

Syngenta Crop Protection, LLC has submitted residue data from a single post-harvest trial conducted during 2012 with fludioxonil on apples. Fludioxonil was applied post-harvest by thermal fogging to Sweet Tango apples in a simulated controlled-atmosphere cold storage warehouse at 0.00490 lb ai/ton of apples (2.45 g/metric ton). Apples in separate rooms were treated with a 99% dry formulation of fludioxonil dissolved and suspended in propylene glycol with diphenylamine (TRT 1) or without diphenylamine (TRT 2). The untreated fruit samples were taken one day prior to application. Four treated samples from each treatment were sampled at an 18- to 20-hour post-treatment interval.

Samples of apple were analyzed for residues of fludioxonil using a liquid chromatograph equipped with tandem mass spectrometers (LC/MS/MS). The limit of quantification (LOQ), based on the lowest level of method validation (LLMV), was 0.01 ppm for fludioxonil in/on apple. The method was adequate for data collection based on acceptable concurrent recoveries. The fortification levels used for concurrent recoveries were adequate to bracket expected residue levels.

Apple samples were stored frozen at ≤–17 °C from collection to extraction for up to 9 days; samples were analyzed on the day of extraction. Adequate storage stability data are available indicating that fludioxonil is stable at ≤–18 °C for up to 28 months in/on grapes (Memo, 12/20/99, W. Donovan, DP# 258870). These data will support the sample storage intervals in the current trial.

Following a post-harvest thermal fogging application of fludioxonil (99% dry formulation suspended in polypropylene glycol) with diphenylamine at 0.0049 lb ai/ton of apples, residues of fludioxonil were 0.391-0.684 ppm (n=4) with a mean of 0.491 ppm (standard deviation of 0.132

ppm) in/on apples collected 18-20 hours post treatment. Residues of fludioxonil were lower in/on apples treated at the same rate without the additive diphenylamine: 0.255-0.404 ppm (n=4) with a mean of 0.339 ppm (standard deviation of 0.066 ppm).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the post-harvest trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 410480].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance, and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Fludioxonil is a contact fungicide, which inhibits protein kinase, leading to reduced fungal growth and development. The chemical structure and nomenclature of fludioxonil and the physicochemical properties of the technical grade of fludioxonil are presented in Tables A.1 and A.2.

TABLE A.1. Fludioxonil Nomenclature.

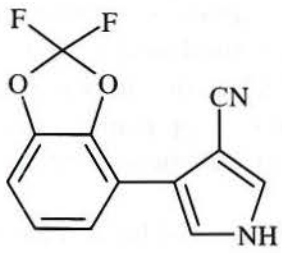
Compound	
Common name	Fludioxonil
Company experimental name	CGA-173506
IUPAC name	4-(2,2-difluoro-1,3-benzodioxol-4-yl)-*1H*-pyrrole-3-carbonitrile
CAS name	4-(2,2-difluoro-1,3-benzodioxol-4-yl)-*1H*-pyrrole-3-carbonitrile
CAS registry number	131341-86-1
End-use products (EP)	CGA173506C (99% dry end-use product formulation; Fludioxonil Technical)

TABLE A.2. Physicochemical Properties of Fludioxonil.		
Parameter	**Value**	**Reference**
Melting point	199.8°C	DP# 348539, D. Rate, 09/10/08
pH	8-9 at 25°C (1% aqueous dispersion)	
Density	1.54 g/cm^3 typical at 23°C	
Water solubility	1.8 mg/L at 25°C	
Solvent solubility	g/L at 20 °C Ethanol 44,000 Acetone 190,000 Toluene 2,700 n-Octanol 20,000 n-Hexane 7.8	
Vapor pressure	2.9 x 10^{-9} mm Hg at 25°C	
Dissociation constant (pK_a)	pK_{a1} <0 pK_{a2} ~14.1	
Octanol/water partition coefficient, Log(K_{OW})	4.12 at 25°C	
UV/visible absorption spectrum	12,384 L mol^{-1} cm^{-1} at 266 nm (neutral solution) 12,327 L mol^{-1} cm^{-1} at 265 nm (acidic solution) 11,790 L mol^{-1} cm^{-1} at 271 nm (basic solution)	

B. EXPERIMENTAL DESIGN

A single small-scale post-harvest study was conducted during 2012 with fludioxonil on Sweet Tango apples. Untreated apples used for post-harvest treatment were obtained from a local grower. As applications were made post-harvest at indoor facilities, variables such as soil type, length of growing season, and weather are not relevant to the current study.

The field phase of the study was conducted at Stemilt Growers (Wenatchee, WA) in research-sized fumigation rooms. Two tests were conducted in separate refrigerated chambers. In each chamber on the day before treatment, 32 individual wooden field bins were prepared for fogging by placing approximately 900 pounds of apples in each bin. In 16 bins, one mesh bag containing 6 apples was placed in the bin with other apples surrounding it; the apples in the mesh bags were the apples that would later be collected as samples. The other 16 crates contained apples without a mesh bag and were used to fill excess space in the fogging chamber for proper room fill and effective fogging. To protect from direct spray of the fogger, a tarp was hung in front of the bins. The apples were left in the fogging chamber overnight to acclimate to the temperature and humidity of the room. Fludioxonil (99% dry formulation; Fludioxonil Technical) was melted and suspended in propylene glycol with diphenylamine (TRT 1; one refrigerated chamber) or without diphenylamine (TRT 2; other refrigerated chamber) and applied at a rate of 0.00490 lb ai/ton of apples (2.45 g/metric ton). The mixture was applied to apples using a Swingtec fogging machine; fogging lasted 3 to 4 minutes. The chamber refrigeration was turned off during fogging and restarted 6 hours after completion of the fogging treatment. Although not stated in the submission, diphenylamine is a chemical used for the control of scald during apple storage.

The study use pattern is presented in Table B.1.2.

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.				
Location: City, State; Year (Trial ID)	Soil characteristics			
	Type	% Organic matter	pH	Cation exchange capacity (meq/100 g)
Not applicable to a post-harvest fogging study.				

TABLE B.1.2. Study Use Pattern on Apples: Post-harvest Application of Fludioxonil.					
Location: City, State; Year	Post-harvest Application				
	Treatment	Formulation	Method	Rate[1] (lb ai/ton) [g ai/metric ton]	Additives
Wenatchee, WA; 2012	TRT 1	99% dry powder suspended in polypropylene glycol	Thermal Fogging	0.00490 [2.45]	Diphenylamine[2]
	TRT 2	99% dry powder suspended in polypropylene glycol	Thermal Fogging	0.00490 [2.45]	None

[1] Application rate was converted to lb ai/ton by the study reviewer.
[2] Deco No Scald DPA Aerosol was added at 1:1.9 (w:w) fludioxonil:diphenylamine.

TABLE B.1.3. Trial Numbers and Geographical Locations.			
	Apple		
		Requested	
NAFTA Growing Zones	Submitted	Canada	U.S.
Not applicable to a proposed post-harvest fogging use.			

B.2. Sample Handling and Preparation

Nine samples (24 fruits/sample), including one untreated, four treated replicates from TRT 1, and four treated replicates from TRT 2 were collected. The untreated sample was taken from the supply of apples one day prior to treatment and treated samples (6 apples/mesh bag x 4 bags/replicate sample) were collected 18 to 20 hours after treatment. Collected samples were placed in insulated containers with dry ice and shipped frozen with dry ice (on the day of collection for treated samples and 2 days following collection for untreated samples) by FedEx (overnight) to Product Safety Labs (Dayton, NJ) for residue analysis. At the analytical facility, samples were maintained under frozen conditions (at approximately –20°C) until extraction; apple samples were quartered and half of the quarters were homogenized in the presence of dry ice in preparation for extraction.

B.3. Analytical Methodology

Samples of apple were analyzed for residues of fludioxonil using an LC/MS/MS method modified from Syngenta Method AG-597B, entitled "Analytical Method for the Determination of CGA173506 in Crops by High Performance Liquid Chromatography including Validation Data." A summary of the method was provided in the submission.

Briefly, an aliquot of the homogenized sample was extracted twice with acetonitrile (ACN):water (9:1, v:v). The extracts were isolated by centrifugation, combined, and diluted to

volume with ACN:water (9:1, v:v). An aliquot was diluted with water for LC/MS/MS analysis. Ion transitions monitored for quantification of fludioxonil were 247.00→126.10 *m/z* and ion transitions for confirmation were 247.00→181.10 *m/z* and 247.00→152.20 *m/z*.

The method was validated prior to and in conjunction with the analysis of study samples. The LOQ, based on the LLMV, was 0.01 ppm in/on apples. The limit of detection (LOD) was defined as 0.003 ppm.

C. RESULTS AND DISCUSSION

Sample storage conditions and durations are reported in Table C.2. Apple samples were stored frozen at approximately –20°C from collection to extraction for 7-9 days; samples were analyzed on the day of extraction. Adequate storage stability data are available indicating that fludioxonil is stable at ≤–18°C for up to 28 months in/on grapes (Memo, 12/20/99, W. Donovan, DP# 258870). These data will support the sample storage intervals in the current trial.

Method validation and concurrent recovery data for the LC/MS/MS method are presented in Table C.1. Samples of apple were fortified with fludioxonil at the LOQ (0.01 ppm), 10x LOQ (0.10 ppm), and 100x LOQ (1.0 ppm) and analyzed using the quantitation and two confirmatory ion transitions. It is noted that one sample was also fortified at the LOD (0.003 ppm) in the method validation but these data are not reported herein. The method was adequate for data collection based on acceptable method validation and concurrent recovery data. All recoveries were within the acceptable range of 70-120%, except for one high concurrent recovery (123%) from apple fortified with fludioxonil at 0.01 ppm and determined using the quantitation ion transition. The fortification levels used in concurrent method recovery were adequate to bracket residue levels. Apparent residues of fludioxonil were nondetectable (<0.003 ppm) in/on the untreated apple samples.

Residue data from the apple post-harvest trial are reported in Table C.3. A summary of the residue data is presented in Table C.4. Following a post-harvest thermal fogging application of fludioxonil (99% dry formulation suspended in polypropylene glycol) with diphenylamine at 0.0049 lb ai/ton of apples, residues of fludioxonil were 0.391-0.684 ppm (n=4) with a mean of 0.491 ppm (standard deviation of 0.132 ppm) in/on apples collected 18-20 hours post treatment. Residues of fludioxonil were lower in/on apples treated at the same rate without the additive diphenylamine: 0.255-0.404 ppm (n=4) with a mean of 0.339 ppm (standard deviation of 0.066 ppm).

TABLE C.1. Summary of Method Validation and Concurrent Recoveries of Fludioxonil from Apples.

Matrix	Fludioxonil Transition Ions[1]	Spike level (ppm)	Sample size (n)	Recoveries[1] (%)	Mean ± std dev[2] (%)
Method Validation					
Apple	Quantitation	0.01	3	105, 115, **123**	114 ± 9.0
		1.0	3	99.3, 102, 109	103 ± 5.0
	Confirmation 1	0.01	3	102, 114, 117	111 ± 7.9
		1.0	3	99.2, 103, 111	104 ± 6.0
	Confirmation 2	0.01	3	93.5, 110, 118	107 ± 12.5
		1.0	3	97.4, 97.4, 107	101 ± 5.5

TABLE C.1. Summary of Method Validation and Concurrent Recoveries of Fludioxonil from Apples.

Matrix	Fludioxonil Transition Ions[1]	Spike level (ppm)	Sample size (n)	Recoveries[1] (%)	Mean ± std dev[2] (%)
Concurrent Recoveries					
Apple	Quantitation	0.01	1	75.0	75.0
		0.10	2	103, 104	104
		1.0	2	92.8, 106	99.4
	Confirmation 1	0.01	1	72.5	72.5
		0.10	2	103, 107	105
		1.0	2	91.0, 107	99.0
	Confirmation 2	0.01	1	76.1	76.1
		0.10	2	101, 106	104
		1.0	2	94.8, 106	100

[1] Quantitation ion transition: 247.00→126.10 *m/z*
Confirmation 1 ion transition: 247.00→181.10 *m/z*
Confirmation 2 ion transition: 247.00→152.20 *m/z*.
Recoveries outside the acceptable 70-120% range are **bolded**.
[2] Standard deviation was not calculated for sample sizes <3.

TABLE C.2. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Apple	Approximately -20	7-9 days	Fludioxonil is stable at ≤–18°C for up to 28 months on grapes.[2]

[1] Actual storage duration from collection to extraction for analysis; samples were analyzed on the day of extraction.
[2] Refer to DP# 258870, W. Donovan, 12/20/99.

TABLE C.3. Residue Data from Post-harvest Apple Trials with Fludioxonil.

Trial: City, State; Year	Apple Variety	TRT[1]	Total Rate (lb ai/ton)	Commodity	PTI[2] (hours)	Fludioxonil Residues (ppm) [average][3]		
						Quantitation Ions	Confirmation 1 Ions	Confirmation 2 Ions
Wenatchee, WA; 2012	Sweet Tango	1	0.0049	Fruit	18-20	0.460, 0.684, 0.430, 0.391 [0.491]	0.436, 0.672, 0.414, 0.379 [0.475]	0.456, 0.716, 0.434, 0.406 [0.503]
		2	0.0049	Fruit	18-20	0.404, 0.318, 0.255, 0.378 [0.339]	0.384, 0.304, 0.244, 0.359 [0.323]	0.404, 0.316, 0.246, 0.383 [0.337]

[1] Treatment 1 = 99% dry powder formulation of fludioxonil suspended in polypropylene glycol with diphenylamine.
Treatment 2 = 99% dry powder formulation of fludioxonil suspended in polypropylene glycol without diphenylamine.
[2] PTI = Post-treatment interval.
[3] Quantitation ion transition: 247.00→126.10 *m/z*
Confirmation 1 ion transition: 247.00→181.10 *m/z*
Confirmation 2 ion transition: 247.00→152.20 *m/z*.

D. CONCLUSION

Adequate documentation was provided for the treatment and laboratory portions of the submitted post-harvest trial for apple. Following a post-harvest thermal fogging application of fludioxonil (99% dry formulation suspended in polypropylene glycol) with diphenylamine at 0.0049 lb ai/ton of apples, residues of fludioxonil were 0.391-0.684 ppm (n=4) with a mean of 0.491 ppm (standard deviation of 0.132 ppm) in/on apples collected 18-20 hours post treatment. Residues of fludioxonil were lower in/on apples treated at the same rate without the additive

diphenylamine: 0.255-0.404 ppm (n=4) with a mean of 0.339 ppm (standard deviation of 0.066 ppm).

An acceptable method was used for residue quantitation and the study is supported by adequate storage stability data.

E. REFERENCES

DP #:	258870
Subject:	PP# 7E04919. Fludioxonil for use on Grapes. Evaluation of Residue Data and Analytical Methods.
From:	W. Donovan
To:	M. Waller
Dated:	12/20/99
MRIDs:	44382322-44382370

F. DOCUMENT TRACKING

RDI: RAB1 Chem. Team: 06/19/2013
Petition Number: none.
DP#: 410480
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